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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,475	11/04/1998	ANNIE FONG	238/046	1830

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/186,475	Fong et al.
Examiner	**Art Unit**
Jennifer Hunt	1642

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 26, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11, 15-21, 23, 24, and 27-32* is/are pending in the application.

4a) Of the above, claim(s) *19-21, 27, and 32* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11, 15-18, 23, 24, and 28-31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. Acknowledgment is made of applicant's cancellation of claim 22, and further applicant's cancellation of the previously effect species of "protein phosphorylation" from generic claim 1. The search was extended with regard to species E "angiogenesis markers" and u-PA was found in the prior art, and thus the claims have been considered only to the extent that they encompass uPA. It is noted that claim 15 needs to be updated with regard to the amendments of claim 1. Claims 1-11, 15-21, 23-24, and 27-32 are pending in the application. Claims 19-21, 27, and 32 have been withdrawn from consideration as being drawn to a non-elected species of invention. An action on the merits of claims 1-11, 15-18, 23-24, and 28-31 follows herein.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Claim Rejections Withdrawn

3. The rejections of claims 1-11, 15-18, 23-24, and 28-31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in light of the amendments thereto.

Claim Rejections Maintained

4. The grounds of rejection of claims 1-11, 15-18, 23-24, and 28-31 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monitoring markers known in the art to correlate to angiogenesis for the purpose of determining an effective dose of an angiogenesis inhibitor, does not reasonably provide enablement for monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL-8, and t-PA, for the purpose of determine an effective dose of an angiogenesis modulator. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to a method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis comprising administering the compound to a patient, monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL-8, and t-PA, constructing a standard curve, and determining the efficacious dose based on the standard curve.

The specification provides generalized theoretical teachings in which a limited number of markers (tissue factor, IL-8, urokinase and tPA) are measured using PCR or ELISA, and a

standard curve is generated to determine how much of the marker is in the isolated sample after a patients have received some sort of unspecified drug treatment. In a second theoretical example, cells are isolated from a patient, then administered a Flk-1 antagonist *in vitro*, and then the cells are eventually lysed and a marker is measured.

Thus the specification fails to provide any guidance or objective evidence that any of the markers which are taught or suggested by the specification in fact correlate to angiogenesis.

Diagnosing and monitoring cancer is an extremely complex process. Often a single factor (such as monitoring a marker) is insufficient to provide an accurate assessment of tumor progress or regression. Further, often a single variable will provide some information about a primary tumor, but fail to provide information regarding metastasis. If the treatment efficacy of a drug is to be measured using a marker, that marker must be carefully selected to be specific and accurate for the determination of the treatment's efficacy. Determination of a dosage using such a marker is even more complex. The marker which is selected must be known to specifically correlate to the progression or regression of disease, taking into account not only tumor size, metastasis, aggressiveness, etc., but also toxicity, quality of life of the patient, etc. (For general guidelines on some of the factors for determining drug dosage, see pages 33-37 of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I). In the instant case, the method fails to account for any of these factors. Further there is no guidance or objective evidence that the broadly recited markers correlate to progression or regression of any cancer, and thus there is no correlation of the broad range of markers to any type of cancer. Further, the most relevant

example provided by the specification (that of a Flk-1 antagonist) refers to an *in vitro* test, which never involves administration of any compound to a patient. Thus it is not clear from applicant's teachings or examples that any marker correlates accurately enough to cancer progression such that it would be effective for determine a dosage curve for a patient.

Thus the claims are broadly drawn, encompassing any one of 6 markers, with no evidence that they would actually correlate to "angiogenesis modulation", particularly in vivo. The state of the art of drug dosage and determination is complex and unpredictable, with many factors which complicate the effective determination of a dose. Therefor one of skill in the art would not be enabled to practice the invention commensurate in scope with the claims.

Applicant agues that the amendments to the claims overcome the grounds of rejection. Applicant's arguments filed 2-26-2002 have been fully considered but are not persuasive.

As set forth above, the specification fails to provide guidance or objective evidence that one of skill in the art would be enabled to use the invention commensurate in scope with the claims.

New Grounds of Rejection

5. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites the limitation "wherein the marker is selected from the group consisting of cell division, cell mortality, cell proliferation, cell death, cell survival, cell differentiation, protein phosphorylation, protein expression, protein glycosylation, mRNA expression, cellular membrane potentia, DNA division, DNA methylation, and post-translational modification.." There is insufficient antecedent basis for this limitation in the claim.

6. Claims 1-6, 9-11, 15-18, 23-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al., US Patent 6,177,401, published January 23, 2001, in view of Hirth, US Patent 5,942,385, and in view of Mandriota et al., The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716, April 1997 (IDS), and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 6,177,401 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, including angiogenesis related to cell proliferation (cancer), specifically the Flk-1 (a receptor involved in angiogenesis) antagonists, comprising administering the compound to a patient, monitoring a marker related to angiogenesis (including protein phosphorylation, or a protein which is expressed in correlation to VEGF), including comparing the marker to a standard, using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 12, line 54-column 16, line 39, column 29, line 49-column 30, line 25, and column 23, lines 30-56).

US Patent 6,177,401 fails to teach a the administration of this monitoring assay to a patient, that the protein which is expressed in correlation to VEGF is uPA, and determination of a correct drug dose using a standard curve.

US Patent 5,942,385 teaches that VEGF and flk-1 can be used to monitor cancer in patients, including in patients blood (which would inherently include monocytes) (see for example, column 6, lines 34-67).

Mandriota et al. teaches that uPA is increased in blood cells in response to VEGF. (Page 9710, column 1.)

Fingl and Woodbury teaches methods of determine efficacious drug dosages, including generating a standard curve.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure flk-1 activity (including protein phosphorylation, or a protein which is expressed in correlation to VEGF), and further use uPA to measure angiogenesis, and further calculate a drug dose using the drug dosage standard curve of Fingl and Woodbury, and one would have been motivated to do so because flk-1 activity (including uPA, a protein which is expressed in correlation to VEGF) correlates to drug efficacy, as taught in 6,177,401, and can be easily measured in numerous body fluids, including blood, as taught in 5,942,385, and because the dosage standard curves were the art standard way of determine an appropriate drug dose.

7. Claims 1-11, 15-18, 23-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al., US Patent 5,792,783, published August 11, 1998, in view of Hirth, US Patent 5,942,385, and in view of Mandriota et al., The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716, April 1997 (IDS), and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 5,792,783 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, including angiogenesis related to cell proliferation (cancer), specifically the Flk-1 (a receptor involved in angiogenesis) antagonist SU 5416 (which is the instant compound a of claim 8), comprising administering the compound to a patient, monitoring a marker related to angiogenesis (protein phosphorylation or expression of a VEGF related protein) using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 2, line 63-column 3, line 40, column 13, lines 5-line 37, column 17, line 65-column 18, line 60, column 22, lines 59-67, and column 32, line 32-column 34, line 44).

US Patent 5,792,783 fails to teach a the administration of this monitoring assay to a patient, including measurement of u-PA, and determination of a correct drug dose using a standard curve.

US Patent 5,942,385 teaches that VEGF and flk-1 can be used to monitor cancer in patients, including in patients blood (which would inherently include monocytes) (see for example, column 6, lines 34-67).

Mandriota et al. teaches that u-PA is increased in blood cells in response to VEGF. (Page 9710, column 1.)

Fingl and Woodbury teaches methods of determine efficacious drug dosages, including generating a standard curve.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure flk-1 activity (including measuring protein phosphorylation or measuring u-PA which correlates to VEGF), and further calculate a drug dose using the drug dosage standard curve of Fingl and Woodbury, and one would have been motivated to do so because flk-1 activity (including protein phosphorylation and u-PA activity) correlates to drug efficacy, as taught in 5,792,783, and can be easily measured in numerous body fluids, including blood, as taught in 5,942,385, and because the dosage standard curves were the art standard way of determine an appropriate drug dose.

8. Claims 1-11, 15-18, 23-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al., US Patent 6,177,401, published January 23, 2001, in view of Hirth, US Patent 5,942,385, and in view of Mandriota et al., The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716, April 1997 (IDS), and further in view of Tang et al., US Patent 5,792,783, published August 11, 1998, and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 6,177,401 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, including angiogenesis related to cell proliferation (cancer), specifically the Flk-1 (a receptor involved in angiogenesis) antagonists, comprising administering the compound to a patient, monitoring a marker related to angiogenesis (including measuring a protein which is expressed in correlation to VEGF, or protein phosphorylation) using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 12, line 54-column 16, line 39, column 29, line 49-column 30, line 25, and column 23, lines 30-56).

US Patent 6,177,401 fails to teach administration of this monitoring assay to a patient, the specific Flk-1 antagonist SU 5416, and determination of a correct drug dose using a standard curve.

US Patent 5,942,385 teaches that VEGF and flk-1 can be used to monitor cancer in patients, including in patients blood (which would inherently include monocytes) (see for example, column 6, lines 34-67).

Mandriota et al. teaches that u-PA is increased in blood cells in response to VEGF. (Page 9710, column 1.)

US Patent 5,792,783 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, specifically the Flk-1 antagonist SU 5416 (which is the instant compound a of claim 8), comprising administering the compound to a patient,

monitoring a marker related to angiogenesis (protein phosphorylation) using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 2, line 63-column 3, line 40, column 13, lines 5-line 37, column 17, line 65-column 18, line 60, column 22, lines 59-67, and column 32, line 32-column 34, line 44).

Fingl and Woodbury teaches methods of determine efficacious drug dosages, including generating a standard curve.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the specific Flk-1 antagonist of US Patent 5,792,783, or the drug dosage standard curve of Fingl and Woodbury with the dosage assay of US Patent 6,177,401, and one would have been motivated to do so because the drug SU 5416 is a known Flk-1 antagonist, as taught by US 5,792,783, and because the dosage standard curves were the art standard way of determine an appropriate drug dose. Further one would have been motivated to administer such to a patient because flk-1 activity (including protein phosphorylation or u-PA activity) correlates to drug efficacy, as taught in 5,792,783.

9. Claims 1-11, 15-18, 23-24, and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al., US Patent 6,177,401, published January 23, 2001, in view of Hirth, US Patent 5,942,385, and in view of Mandriota et al., The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716, April 1997 (IDS), and further in view of Tang et

al., US Patent 5,792,783, published August 11, 1998, and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 6,177,401, US Patent 5,792,783, Mandriota et al., US Patent 5,942,385, and Fingl and Woobury teach as set forth supra. US Patent 6,177,401, US Patent 5,792,783, Mandriota et al., US Patent 5,942,385, and Fingl and Woobury fail to teach that the specific efficacious dosages and standard curves.

Determination of specific optimal standard dosages/standard curves represents optimization of the known dosage curve methods and would be a matter of routine experimentation, given what is known in the art, exemplified in US Patent 6,177,401, US Patent 5,792,783, Mandriota et al., US Patent 5,942,385, and Fingl and Woobury.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was alter the methods of US Patent 6,177,401, US Patent 5,792,783, Mandriota et al., US Patent 5,942,385, and Fingl and Woobury to generate the specific standard curves of the instant claims and one would have done so as means of determining the most effective dose, based on the teachings and knowledge in the prior art.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

May 20, 2002

SHEELA HUFF
PRIMARY EXAMINER